REMARKS

AMENDMENTS TO THE SPECIFICATION

Support for the amendments to the specification may be found in the instant application as originally filed. No new matter has been added.

A Substitute Specification was submitted to replace the instant specification which contains amendments that correct typographical errors and amendments designed to denote recognized trademarks, as summarized in section (I)(b) herein. In accordance with MPEP 608.01(q), Applicants state that the Substitute Specification does not contain no new matter.

I. Miscellaneous

a. Domestic Priority

The Examiner has objected to Applicants claim for domestic priority under 35 U.S.C. §§ 119(e) and 120 for Claims 41 and 42. More particularly, the Examiner alleges:

> Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:
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> The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later- filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.,* 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).
>
> The disclosure of the prior-filed application, Application No. 60/350,061, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.
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> The instant claims recites a method of using expression profile of certain polynucleotides or polypeptides to indicate a cell's sensitivity to a protein kinase inhibitor. The instant claims. recites several specific SEQ ID Nos such as SEQ ID NO: 204. However, the provisional application 60/350,061 does not appear to have support for the claimed method of using polypeptides with the listed SEQ ID Nos in the instant claims 41 and 42. For example, SEQ ID No:204 of the instant claim 1 is .drawn to a polypeptide sequence. However, SEQ ID NO: 204 listed in the provisional application recites a polynucleotide sequence. The polynucleotide sequence recited in SEQ ID NO204 of the provisional also does not appear to be structurally the same to the polynucleotide of the instant claim 41 that encodes for the polypeptide of SEQ ID No:204 of the instant application. The said subject matter does not obtain the priority date of the provisional application, 60/350,061.
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> Thus, the effective filing date for the said subject matter of the instant claims is *1/17/2003.*

Applicants disagree with the Examiner's allegation and point out that USSN 60/350,061 on which Applicants rely for priority, does in fact disclose both the polypeptide sequence of SEQ ID

NO:204, as well as SEQ ID NO:3, the polynucleotide that encodes this polypeptide sequence, although the SEQ ID NOs for each differ from the SEQ ID NOs assigned to these sequences in the instant specification. Specifically, Applicants point out that SEQ ID NO:204 is disclosed in USSN 60/350,061 as SEQ ID NO:236, and SEQ ID NO:3 is disclosed in USSN 60/350,061 as SEQ ID NO:36. An alignment between these sequences as disclosed in USSN 60/350,061 and the instant specification are provided in Exhibits A and B, for the convenience of the Examiner.

Accordingly, the instant specification is entitled to the benefit of the January 18, 2002 priority because USSN 60/350,061 does, in fact, provide support for Claims 41 and 42, and hence for new Claims 43 and 44, and the Examiner's objection to the priority claim should be withdrawn.

b. Objections to the Specification

The Examiner has objected to the specification stating:

> The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. MPEP 608.01.

In response, Applicants have searched the specification for embedded hyperlinks, typographical errors, and trademarks, and made any required changes to the Substitute Specification, submitted herewith.

Applicants believe all of the Examiner's objections to the specification have been overcome in consideration of these amendments.

b. Objection to the Claims

The Examiner has objected to Claim 42 stating:

> Claim 42 is objected to because of the following informalities: The phrase "a expression product" in line 2 of the said claim should be amended to recite "an expression product". Appropriate correction is required.

In response, Applicants have cancelled Claim 42 and presented new Claim 44 which conforms to the Examiner's recommendation. Applicants assert the Examiner's objection to Claim 42 has been rendered moot in consideration of Applicants cancellation of this claim, and that new Claim 44 is not subject to this objection.

II. Rejections under 35 U.S.C. § 112, First Paragraph

a. The Examiner has rejected Claims 41 and 42 under 35 U.S.C. § 112, first paragraph, alleging these claims fail to comply with the written description requirement on the ground they contain new matter. More particularly, the Examiner alleges:

> Claims 41 and 42 have been newly added and recite "while decreased expression of said gene expression product in said sample relative to a standard is indicative of resistance to a protein tyrosine kinase inhibitor". However, the instant specification does not appear to provide support for the claimed "decreased expression of said gene expression.., is indicative of resistance". The citations pointed out by applicants (Reply, filed on 9/6/07) for support of the newly added claims do not appear to offer support for the said specific citation. For example Applicants pointed to the Tables (e.g. 3-6 and 10-12) of the instant specification, which Tables only indicate that the listed genes are "highly expressed" (i.e. increased expression) in resistant cells (see Table 12, for example). It is not clear which specific passage of the instant specification discloses that "decreased expression" indicates resistance.
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> If Applicant believes this rejection is in error, applicant must disclose where in the specification support for the entire scope of the amendment(s) and/or new claims can be found. As a result, Claims 41 and 42 represent new matter.

Applicants disagree with the Examiner's allegation and assert the instant specification does provide the requisite teachings to convince a skilled artisan that the inventor(s) in fact had possession of the claimed invention at the time the application was filed. Applicants point out that the predictor polynucleotides and polypeptides disclosed in the instant specification were identified by detecting those polynucleotides and polypeptides that were highly expressed in colon cancer cell lines that were either sensitive or resistant to protein tyrosine kinase inhibitors (see pages 20-22 of the specification). However, while the overexpression status of such polynucleotides and polypeptides was a criterion for identifying the individual predictor sequences, the lack of overexpression of one type of predicter (e.g., a sensitive marker) in a particular cell would be interpreted as that cell having a phenotype consistent with the opposite phenotype (e.g., resistant). For example, the specification teaches the following:

> Expression profiling data of 12,558 polynucleotides and polypeptides represented on the HG-U95Av2 array for thirty-one untreated colon cell lines were obtained and preprocessed as described in Example 1, Methods. The preprocessed data were analyzed using the K-mean Nearest Neighborhood (KNN) algorithm to identify polynucleotides and polypeptides whose expression patterns were strongly correlated with the drug resistance/sensitivity classification. (Table 2). ***An "idealized expression pattern" corresponds to a gene that is uniformly high in one class (e.g., sensitive) and uniformly low in the other class (e.g., resistant).*** Initially, a KNN analysis was performed in which a correlation coefficient was obtained for each gene. (emphasis added)

(see paragraph beginning on line 24, page 20). Thus, for any given predicter polynucleotide or polypeptide that is overexpressed in sensitive cancer cell lines, for example, it is expected that the polynucleotide or polypeptide will be expressed at a correspondingly lower level in a resistant cancer cell line. The basis for this dichotomy is due, in part, to the fact that the overexpressed sensitive markers are believed to be substrates for protein tyrosine kinases. For example, the specification teaches the following:

> ***A number of the polynucleotides and polypeptides as described herein (Tables 3-6) are known to be substrates for the src tyrosine kinase family, e.g., caveolin-1, caveolin-2, phosphoinositide 3-kinase, etc., (M.T. Brown and J.A. Cooper, 1996, Biochemica et Biophysica Acta, 1287:121-149). This is expected, since polynucleotides and polypeptides that contribute to a high predictor accuracy are likely to play a functional role in the pathway that is being modulated.*** For example, Herceptin therapy (i.e., antibody that binds to the Her2 receptor and prevents function via internalization) is indicated when the Her2 gene is overexpressed. ***It is unlikely that a therapy will have any therapeutic effect if the target enzyme is not expressed.*** (emphasis added)

(see paragraph beginning on line 14, page 28). As a consequence, Applicants assert that because of this inverse relationship between overexpression of a sensitive marker in a sensitive cell line to this markers concomitant low expression in resistant cell lines, that one skilled in the art would credibly believe that Applicants were in possession of a method of predicting whether a cell is predicted to be resistant to a protein tyrosine kinase inhibitor based upon the decreased expression of a sensitive informative gene.

Applicants remind the Examiner that there is no requirement for a limitation to be explicitly supported word-for-word in the specification in order for the written description requirement to be

satisfied. Rather, the M.P.E.P. states that claim limitations may be supported in the specification through "express, implicit, or inherent disclosure..." and that "there is no *in haec verba* requirement" (see M.P.E.P. 2163(I)(B))(emphasis added). The M.P.E.P. teaches that whether the written description requirement is met turns on whether "...a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification...See, e.g., Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, USPQ 391, 395 (CCPA 1972)(stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient"). (see M.P.E.P. 2163(II)(A)(3)(a))(emphasis added).

Accordingly, Applicants request that the Examiner's rejection of Claims 41 and 42 under 35 U.S.C. § 112, first paragraph be withdrawn and not be applied to new Claims 43 and 44.

III. Rejections under 35 U.S.C. § 112, Second Paragraph

a. The Examiner has rejected Claims 41 and 42 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner alleges:

> The claim language of Claims 41 and 42 are unclear and indefinite. For example, Claims 41 and 42 recite "while decreased expression of said gene expression product in said sample relative to a standard is indicative of resistance to a protein tyrosine kinas inhibitor", which recitation seems to contradict the definition and disclosure of the instant specification. The instant specification, for example, lists "polynucleotides" that are used to indicate "sensitivity/resistance" of cells to kinase inhibitors in various Tables. The instant specification discloses the "polynucleotides" are all "highly expressed" (i.e. increased expression) in resistant cells (see Table 12, for example), which are in direct contradiction with the recitation "decreased expression.., indicative of resistance" of the instant claim. Thus, one of ordinary skill in the art . would not be able to apprise the metes and bounds of the Claimed invention. See MPEP 2173.03.

Applicants disagree with the Examiner's allegations on the ground they are misrepresentative of the claimed invention. As noted *supra*, the predicter polynucleotides and polypeptides disclosed in the instant specification were identified by detecting those polynucleotides and polypeptides that were highly expressed in either sensitive or resistant colon cancer cell lines to protein tyrosine kinase inhibitors (see pages 20-22 of the specification). Thus, polynucleotides and polypeptides that were reproducibly overexpressed in sensitive cell lines were considered sensitive predictors, while

polynucleotides and polypeptides reproducibly overexpressed in resistant cell lines were considered resistant predictors, based upon the teachings of the instant specification. The distinction between whether any given predicter polynucleotides and polypeptides are deemed to be a sensitive predictor or a resistant predictor is clearly shown in the "Highly Expressed Cells (Sensitive or Resistant)" column of Tables 3, 4, 5, 6, 10, 11, and 12.

In addition, the use of the language "increased expression of said expression product in said sample relative to a standard is indicative of sensitivity" and the use of the language "decreased expression of said gene expression product in said sample relative to a standard is indicative of resistance" within the same claim is not a direct contradiction, but rather is consistent with the nature of the predictor polynucleotides and polypeptides as applied to the claimed assay. Specifically, Applicants noted *supra* that overexpression was used as a criterion for selecting the predictor polynucleotides and polypeptides from sensitive or resistant cell lines. Secondly, Applicants also noted *supra* that the selected predictor polynucleotides and polypeptides are likely to be substrates for protein tyrosine kinase inhibitors. The selection of overexpressed predictors in sensitive cell lines is expected because they "are likely to play a functional role in the pathway that is being modulated" (see paragraph beginning on line 14, page 28). In addition, the absence of expression of a sensitive predictor would likely be diagnostic for a resistant phenotype, and not a sensitive phenotype, because a compound targeting a specific protein, for example, would not be expected to "...have any therapeutic effect if the target enzyme [was] not expressed". (see paragraph beginning on line 14, page 28). The diagnostic method example cited in the specification for whether a patient should receive Herceptin therapy or not is helpful in understanding the above relationship because only individuals who test positive for Her2 overexpression, the sensitive marker in that case, should receive Herceptin, while those that do not test positive for Her2 overexpression are not good candidates to receive Herceptin because the sensitive marker is the target of the therapy. Thus, having a diagnostic method for predicting whether any given colon cancer cell is **sensitive** to a protein tyrosine kinase inhibitor be based upon whether a sensitive marker (the claimed BMP2 is a sensitive marker as shown in Table 3, 4, 5, 6, 10, 11, and 12) is **overexpressed** or not, while also including its logical corollary within the method (i.e., determining whether any given colon cancer cell is **resistant** to a protein tyrosine kinase inhibitor be based upon whether the expression level of a sensitive marker (the claimed BMP2 is a sensitive marker as shown in Table 3, 4, 5, 6, 10, 11, and 12) is **decreased** or not is completely consistent and one skilled in the art would naturally understand the metes and bounds of the claimed invention.

Accordingly, Applicants request that the Examiner's rejection of Claims 41 and 42 under 35 U.S.C. § 112, second paragraph be withdrawn and not be applied to new Claims 43 and 44.

IV. Rejection under 35 U.S.C. § 102(b)

a. The Examiner has rejected Claim 41 under 35 U.S.C. § 102(b) as being anticipated by Imai et al. (Pathology International. Vol. 51: 643-648; 8/2001). More particularly, the Examiner alleges:

> The instant claims recite "A method of identifying colon cancer cells that are either resistant or sensitive to a protein tyrosine kinase inhibitor comprising the step of determining the expression profile of an expression product from at least one informative polynucleotide in a colon cancer sample, wherein said at least one informative polynucleotide is the polynucleotide encoding bone morphogenetic protein 2 (SEQ ID NO:204), and wherein increased expression of said expression product in said sample relative to a standard is indicative of sensitivity to a protein tyrosine kinase inhibitor, while decreased expression of said gene expression product in said sample relative to a standard is indicative of resistance to a protein tyrosine kinase inhibitor".
>
> The recitation "identifying colon cancer cells that are either resistant or sensitive to a protein tyrosine kinase inhibitor" in the preamble of clm 41 is construed as intended uses of the instant claimed method for the purpose of the following prior art rejections, because the said recitations do not appear to impart structural limitations to the claimed method steps. See MPEP 2111.02 II: "If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999)."
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> In this case, the body of the claims set forth all the method structural limitation of the claimed method. The body of the claim (e.g. Claim 41) recites "determining the expression profile of an expression product from at least one informative polynucleotide in a colon cancer sample.. ?' That is the body of the claim recites all the required method steps/reagents including "determining the expression profile", "SEQ ID NO:204", "a colon cancer sample", etc. The recitation of "identifying colon cancer cells that are either resistant or sensitive to a protein tyrosine kinase inhibitor" does not offer additional structural limitation to the claimed method, and only seems to provide the "intended result" (or use) of the process step in the body of the instant claims. That is the

"determining expression profile" step of the specific recited polynucleotides (e.g. polynucleotide encoding SEQ ID NO:204) in a colon cancer cell would result in the *identification* of the "colon cancer" as either "resistant or sensitive to a protein tyrosine kinase inhibitor". This claim interpretation is supported by the instant specification where a cell's resistance/sensitivity to a kinase inhibitor is correlated to various gene expression profiles (e.g.p.19, lines 11+; Tables).

In addition, the underlined region of the recitation "wherein increased expression of said expression product in said sample relative to a standard is indicative of sensitivity to a protein tyrosine kinase inhibitor, while decreased expression of-said gene expression product in said sample relative to a standard is indicative of resistance to a protein tyrosine kinase inhibitor" in the instant claims 41 and 42 also do not appear to provide additional structural limitations such as additional method steps/reagents.

See MPEP 2106 II: "Language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation." (emphasis in original);

See also MPEP 2111.04: "Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:
(A) "adapted to" or "adapted for" clauses;
(B) "wherein" clauses; and
(C) "whereby" clauses."
"... However, the court noted (quoting Minton v. Nat '1 Ass 'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 fled. Cir. 2003)) that a 'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'". (emphasis added).

In this case, the phrase "relative to a standard" (i.e. comparing the sample cell gene expression to a standard) can be construed as another "process step" that is "positively recited". The recitations such as "indicative of sensitivity to a protein tyrosine kinase inhibitor" simply expresses the intended result of the a process step positively recited".

Therefore, the instant claim 41 can be construed to recite a method comprising the following method steps/reagents:

A.) determining the expression profile of at least one polynucleotide comprising a polynucleotide encoding for a protein of SEQ]D NO: 204 (or bone morphogenic protein 2);

B.) comparing the expression profile of A) to "a standard"..

The following art rejection is discussed in light of the above claim interpretation.

Imai et al, throughout the publication, teach monitoring gene expression profile of various genes in colon cancer samples (e.g. Abstract). The reference teaches determining the gene expression of various bone morphogenetic proteins (BMPs) in colon tumors and surrounding cells from colon tissues by using immunohistochemical staining of the proteins (i.e. expression products) (e.g. Figure 1; pp.644-645), which read on the steps of determining gene expression profile of an expression product of an informative polynucleotide as recited in claim 41.

The reference also teaches comparing the gene expression of BMP-2 gene in various cells such as tumor cells and "mesenchymal fibroblast cells" (e.g. Figure 4; p.645, para 2), which read on the comparing with "a standard" of elm 41 because the mesenchymal fibroblast cells can be considered as a standard as the term "a standard" is broadly used in the instant disclosure. The reference also inherently teaches BMP-2 has the amino acid sequence listed in SEQ ID NO:204, as evidenced by the instant disclosure reciting BMP-2 protein has the sequence listed in SEQ ID NO:204 (See p.104, Table 3 of the spec.). The reference teaches that the Bone Morphogenetic Proteins expressed are human proteins (e.g. Abstract), and the instant specification also teaches that the BMP-2 protein is of human origin as reflected by its GenBank accession number "M22489" (see p.104, Table 3) and citation in the instant Sequence Listing. Thus, the BMPr2 protein of the reference inherently comprise the sequence recited in SEQ ID NO:204 without evidence to the contrary.

As discussed above, the recitation "wherein increased expression ... is indicative of sensitivity to a protein tyrosine kinase inhibitor, while decreased expression ..." is construed as intended use or result of the instant claimed method. See MPEP 2111.04: "However, the court noted (quoting Minton v. Nat '1 Ass 'n of Securities Dealers, Inc., 336 F.3d 1373, I381, 67 USPQ2d 1614, 1620 fled. Cir. 2003)) that a 'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" (emphasis added).

Applicants disagree with the Examiner's allegations and assert the rejection of Claims 41 and 42 under 35 U.S.C. § 102(b) is improper on account of the Examiner's basis for the rejection being an improper construction of the law. The Examiner cites *Minton* for the proposition that "a whereby clause in a method claim is not given weight when it simply expresses the intended

result of a process step positively recited",[1] and uses this as a basis for attempting to establish that the "wherein" clauses within Claim 41 do not limit the scope of the claim. Applicants disagree with this construction and assert it is in error. In *Minton*, the Court of Appeals of the Federal Circuit reviewed the Eastern District of Texas claim construction of a claim directed to a method of trading securities between individuals.[2] The claim in question contained a "whereby" clause that stated "whereby the security is traded efficiently between the first individuals and the second individual". The Federal Court upheld the District Court's decision to not give weight to the "traded efficiently" phrase within the whereby clause on the ground it merely represented "the result of the executing step", but did not "inform the mechanics of how the trade is executed".[3] It is worth noting that the Federal Circuit cited *Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n* to support its conclusion on this specific point.[4] In *Texas Instruments*, the Federal Circuit construed the language of a similar "whereby" clause and held that a "'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claims".[5] The whereby clause in that case stated "whereby the fluid will not directly engage the device and electrical connection means at high velocity, and the conductors will be secured against appreciable displacement by the fluid". The Federal Circuit commented that such a whereby clause "merely describe[d] the result of arranging the components of the claims in the manner recited in the claims: the fluid does not directly engage the device and the electrical connection means because the gate through which the fluid enters is remote from them; the conductors are secured against appreciable displacement by the fluid because they are clamped in notches by the upper and lower halves of the mold die."[6] Thus, the rule that can be surmised from the combination of both the *Milton* and *Texas Instruments* cases would be that in the specific circumstance in which a whereby clause merely states the result of the limitations (i.e., what would happen as a direct consequence of practicing the method steps), the whereby clause does not constitute a limitation of the claims. In contrast, when the whereby clause includes more than the mere result of the limitations, the whereby clause will be considered to add a limitation to the claims.

Applying the *Milton* and *Texas Instruments* rule(s) to the instant invention does not, however, result in the conclusion reached by the Examiner because the wherein clauses of Claim

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[1] *Milton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003).
[2] *Id.* at 1374 and 1380.
[3] *Id.* at 1381.
[4] *Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1172 (Federal Cir. 1993).
[5] *Id.* at 1171-2.
[6] *Id.*

41 do not merely list the result of performing the method step, but rather also includes (i) the specific sequence to be used as the informative polynucleotide (BMP2 – SEQ ID NO:204 in this case), and (ii) the determinative interpretation of the result (i.e., if the result is increased expression, is indicative cells are sensitive; but if the result is decreased expression, then is indicative cells are resistant). Thus, because merely performing the step of measuring an expression profile of least one informative polynucleotide in a colon cancer sample would not lead to (i) the identity of the informative polynucleotide, nor (ii) the determinative interpretation of the expression result obtained (i.e., are the cells sensitive or resistant), both of the wherein claims of Claim 41 would be construed as a claim limitation.

Accordingly, Applicants disagree with the Examiner's allegations and assert that Imai et al. is not a proper reference under 35 U.S.C. § 102(b) on account of it failing to teach all of the elements of the claimed invention. According to the MPEP, "[a] *claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."* Verdegaal Bros. v. Union Oil Co. of California, *814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)(MPEP 2131).* As noted *supra*, Imai et al. fails to teach the elements of Claim 41 directed to interpreting the result of the expression profile of a colon cancer sample such that increased expression of BMP2 (SEQ ID NO:204) is indicative of sensitivity to a protein tyrosine kinase inhibitor, whereas decreased expression is indicative of resistance to a protein tyrosine kinase inhibitor. Accordingly, Imai et al. is not a proper reference under 35 U.S.C. § 102(b).

In addition, Applicants remind the Examiner that she is not permitted to impute or infer an element into a reference where the reference otherwise fails to teach that element. Rather, in order for a reference to be a proper reference under 35 U.S.C. § 102, "[t]he *identical invention* must be shown in as *complete detail as is contained in the ... claim*." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).(MPEP 2131)(emphasis added). Because Imai et al. fails to teach the elements of Claim 41 directed to interpreting the result of the expression profile of a colon cancer sample such that increased expression of BMP2 (SEQ ID NO:204) is indicative of sensitivity to a protein tyrosine kinase inhibitor, whereas decreased expression is indicative of resistance to a protein tyrosine kinase inhibitor, Imai et al. is not a proper reference under 35 U.S.C. § 102(b).

Accordingly, Applicants assert the Examiner's rejection of Claim 41 under 35 U.S.C. § 102(b) is improper because Imai et al. fails to teach all of the elements of this claim and respectfully request that the Examiner withdraw the same. In addition, because Claim 42 depends from Claim

41, Applicants assert the Examiner's rejection of Claim 42 under 35 U.S.C. § 102(b) is also not proper and should be withdrawn.

In addition, Applicants assert that Imai et al. is not a proper reference under 35 U.S.C. § 102(b) on the ground that it fails to represent an enabling reference. According to the MPEP, "[t]he disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*<, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003)(MPEP 2121.01). Thus, in the unlikely event the Examiner were to maintain her allegation that the elements of the claimed invention are anticipated by Imai et al., Imai et al. would still fail as a proper reference under 35 U.S.C. § 102(b) on the basis it fails to teach how one skilled in the art could actually make and use the methods disclosed in Imai et al. for the claimed method of predicting whether a colon cancer cell would be expected to be sensitive or resistant to a protein tyrosine kinase inhibitor. The skilled artisan would readily appreciate that there is a fundamental difference between merely determining the expression profile of any given polynucleotide or polypeptide (i.e., as taught in Imai et al.), and a method of predicting whether a cell is likely to be sensitive or resistant to a specific class of compounds, in this case protein tyrosine kinase inhibitors (i.e., the invention currently claimed). However, no where does Imai et al. teach a method of **predicting** whether a compound is likely to be sensitive or resistant to protein tyrosine kinase inhibitors based upon the expression profile of any polynucleotide or polypeptide, let alone BMP2. Rather, Imai et al. merely lists the expression profile of several BMP genes in colon carcinoma of a 50 year old adenocarcinoma patient – but nothing more. Only the instant specification makes the unique association between BMP2 expression and its use in predicting whether a colon cancer cell would be expected to be sensitive or resistant to a protein tyrosine kinase inhibitor.

Accordingly, Applicants assert the Examiner's rejection of Claim 41 under 35 U.S.C. § 102(b) is improper because Imai et al. fails to represent an enabling reference and respectfully request that the Examiner withdraw the same. In addition, because Claim 42 depends from Claim 41, Applicants assert the Examiner's rejection of Claim 42 under 35 U.S.C. § 102(b) is also not proper and should be withdrawn.

Nonetheless, in the sole interest of facilitating prosecution, Applicants have cancelled Claims 41 and 42 and replaced them with new Claims 43 and 44. New Claim 43 presents the elements of prior Claim 41 in a new format that more clearly delineates the method steps. New Claim 44 also

presents the elements of prior Claim 42 in a new format that more clearly delineates the method steps. Accordingly, even if the Examiner's rejection of Claims 41 and 42 under 35 U.S.C. § 102(b) were deemed proper, Applicant's believe that the foregoing arguments, and amendments presented herein, would overcome the Examiner's rejections and respectfully request that they be withdrawn and not be applied to new Claims 43 and 44.

V. Rejection under 35 U.S.C. § 103(a)

a. The Examiner has reminded Applicants of its obligations under 35 U.S.C. § 103(a) on account of the current applicant naming joint inventors. More particularly, the Examiner alleges:

> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

In response, Applicants point out that the instant specification was commonly owned at the time the invention claimed in this application were made. In particular, Applicants bring to the attention of the Examiner the assignments recorded on April 29, 2005, on reel 016184 and frame 0502 for USSN 10/501,035. Accordingly, Applicants assert these assignments evidence that the inventions were commonly owned at the time the claimed inventions in these applications were made.

b. The Examiner has rejected Claim 41 under 35 U.S.C. § 103(a) as being unpatentable over Imai et al (Pathology International. Vol.51: 643-648; 8/2001; Publication date is 1 year prior to the above said effective filing date of 1/17/03.).), in view of Roth et al (US 20020051978; 5/2/02; filed on 2/16/01; or earlier priority date). More particularly, the Examiner alleges:

> The instant claims are construed the same as the discussed above under the rejection over the Imai reference alone.

Imai et al, throughout the publication, teach monitoring gene expression profile of various genes in colon cancer sample, as discussed above.

Imai et al do not explicitly teach using an additional polynucleotide with sequences recited in the specific SEQ ID Nos as recited in clm 42.

However, Roth et al, throughout the publication, teach identifying cells that are sensitive to cancer therapeutic agents using gene expression profile. (e.g. Abstract). The reference teaches measuring gene expression in various cancer cells including colon/colorectal tumor cells (e.g. p.5, [0061]). The reference also teaches the gene markers used for assessing gene expression profile to determine drug sensitivity includes the polynucleotide of GenBank accession number "D13413" (e.g. Tables 6 and 8), which the GenBank accession number D13413 corresponds to the polynucleotide encoding the protein of the instant SEQ ID No:247 of elm 42, as evidenced by Table 3 of the instant specification. The reference also teaches that the gene with accession number D13413 is differentially expressed in cells that have differential response to cancer therapeutic drugs. (e.g. Table 6; p.29).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to determining gene expression profiles of various genes of interest.

A person of ordinary skill in the art would have been motivated at the time of the invention to monitor gene expression profile of a polynucleotide With Gerd3ank accession number D 13413 (or the polynucleotide encoding for SEQ ID NO:247) in colon/colorectal cancer cells, because the marker, D13413 provides the advantages of having differential gene expression profile in cells with different reactivity (sensitivity or resistance) to cancer therapeutic agents, as taught by Roth et al. In addition, one of ordinary skill in the art would have been motivated at the time of the invention to use D 13413 polynucleotide in addition to BMP-2 gene for achieving the predictable result of measuring differential gene expression profile in colon/colorectal cancer cells.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since both Imai et al and Roth et al have demonstrated the success of measuring gene expression profiles (e.g. measuring gene expression products) in colon cancer cells.

Applicants disagree with the Examiner's allegation and assert that the invention encompassed by Claims 41 and 42 is not obvious over Imai et al. in view of Roth et al. and assert the Examiner's rejection of these claims under 35 U.S.C. § 103(a), is in error. Applicants remind the

Examiner that before a rejection of a claim under 35 U.S.C. § 103(a) can properly be made, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP 2143). Neither Imai et al. nor Roth et al. alone or in combination, teach all of the limitations of Claim 41. Specifically, neither of these publications teaches a method for predicting whether a colon cancer cell will be resistant or sensitive to a protein tyrosine kinase inhibitor by measuring the expression level of the BMP2 receptor. Secondly, neither application even mentions the term protein tyrosine kinase inhibitor, let alone protein tyrosine kinase. As a consequence, Applicants submit that the Examiner's burden to establish a prima facie case of obviousness under 35 U.S.C. § 103(a) is not satisfied and accordingly should be withdrawn and not be applied to new Claim 43. In addition, because Claim 42 depends from Claim 41, Applicants assert the Examiner's rejection of Claim 42 under 35 U.S.C. § 103(a) is also not proper and should be withdrawn and not be applied to new Claim 44.

c. The Examiner has rejected Claim 41 under 35 U.S.C. § 103(a) as being unpatentable by Shyjan et al (US 20020006613; .1/17/2002; 1/17/2002; filed 8/13/2002; or earlier priority date), in view of Imai et al (Pathology International. Vol.51: 643-648; 8/2001) and Roth et al (US 20020051978; 5/2/02; filed on 2/16/01; or earlier priority date). More particularly, the Examiner alleges:

> The instant claims are construed the same as the discussed above under the rejection over the Imai reference alone.
>
> Shyjan et al, throughout the publication, teach Using gene expression profile of markers (or nucleic acids) to determine if cancer cells are sensitive or resistant to a therapeutic agent. (e.g. Abstract). The reference teaches determining gene expression levels from cancer cell samples (e.g.p.1, [0008]+; claims 1+; p.3, [0030]+) by measuring gene expression products such as mRNA levels (e.g. pp.5-6, [0048]+), which read on the steps of determining gene expression profile of an expression product of an informative polynucleotide as recited in elm 41. The reference also teaches comparing the expression profile of the genes of colon cancer cell tine~ to standards (e.g. pp.19-20; [0212]).
>
> Shyjan et al do not explicitly teach monitoring the .gene expression of BMP-2 (i.e. SEQ ID NO:204) as recited in elm 41, and another additional polynucleotide with sequences recited in the specific SEQ ID Nos as recited in elm 42.

However, Imai el al, throughout the publication, teach monitoring gene expression profile of various genes in colon cancer samples, as discussed above. The Imai reference also teaches that BMP-2 gene is differentially expressed in colon tumor tissues.

Roth et al, *throughout* the publication, teach *identifying* cells that are sensitive *to* cancer therapeutic agents using gene expression profile. (e.g. Abstract). The reference teaches measuring gene expression in various cancer cells including colon/colorectal tumor cells (e.g. p.5, [0061]). The reference also teaches the genemarkers used for assessing gene expression profile to determine drug sensitivity includes the polynucleotide of GenBank accession number "D13413" (e.g. Tables 6 and 8), which the GenBank accession number D13413 corresponds to the polynucleotide encoding the *protein* of the instant SEQ *ID* No:247 of elm 42, as evidenced by Table 3 of the instant specification. The reference also teaches that the gene with accession number D13413 is differentially expressed in cells that have differential response to cancer therapeutic drugs. (e.g. Table 6; p.29). Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to determining gene expression profiles of various genes of interest in colon cancer tissues.

A person of ordinary skill in the art would have been motivated at the time of the invention to monitor gene expression profile of BMP-2 gene in colon/colorectal cancer cells, because BMP-2 gene provides the advantage as a useful and unique marker that is differentially expressed in the colon tissues.

A person of ordinary skill in the art would have been motivated at the time of the invention to monitor gene expression profile of a polynucleotide with GenBank accession number D13413 (or the polynucleotide encoding for SEQ ID NO:247) in colon/colorectal cancer cells, because the marker, D13413 provides the advantages of having differential gene expression profile in cells with different reactivity (sensitivity or resistance) to cancer therapeutic agents, as taught by Roth et al. In addition, one of ordinary skill in the art would have been motivated at the time of the invention to use D13413 polynucleotide in addition to BMP-2 gene for achieving the predictable result of measuring differential gene expression profile in colon/colorectal cancer cells. A person of ordinary skill in the art would have *reasonable* expectation of success of achieving such *modifications* since Shyjan et al, Imai et al and Roth et al have demonstrated the success of measuring various gene expression profiles (e.g. measuring gene expression products) in colon cancer cells.

Applicants disagree with the Examiner's allegation and assert that the invention encompassed by Claims 41 and 42 is not obvious over Shyjan et al., in view of Imai et al. and Roth

et al. and assert the Examiner's rejection of these claims under 35 U.S.C. § 103(a), is in error. Applicants remind the Examiner that before a rejection of a claim under 35 U.S.C. § 103(a) can properly be made, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP 2143). Neither Shyjan et al., Imai et al. nor Roth et al. alone or in combination, teach all of the limitations of Claim 41. Specifically, neither of these publications teaches a method for predicting whether a colon cancer cell will be resistant or sensitive to a protein tyrosine kinase inhibitor by measuring the expression level of the BMP2 receptor. Secondly, neither application even mentions the phrase "protein tyrosine kinase inhibitor", let alone "protein tyrosine kinase". As a consequence, Applicants submit that the Examiner's burden to establish a prima facie case of obviousness under 35 U.S.C. § 103(a) is not satisfied and accordingly should be withdrawn and not be applied to new Claim 43. In addition, because Claim 42 depends from Claim 41, Applicants assert the Examiner's rejection of Claim 42 under 35 U.S.C. § 103(a) is also not proper and should be withdrawn and not be applied to new Claim 43.

VI. Provisional Non-statutory Double Patenting Rejection

a. The Examiner has provisionally rejected Claims 41 and 42 under the judicially created doctrine of non-statutory double patenting. More particularly, the Examiner alleges:

> Claims 41 and 42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 41, 43 and 44 of copending Application No10/348,119 (US 20070166704). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed method of the '119 co-pending application read on the instant claimed invention.
>
> Claim 41 of the '119 application recites: "A method of identifying colon cancer cells that are either resistant or sensitive to a protein tyrosine kinase inhibitor comprising the step of determining the expression profile of an expression product from an informative polynucleotide predictor set in a colon cancer sample, wherein said informative polynucleotide predictor set consists of: SEQ ID NO: 1... SEQ ID NO:3...", which read on the claim limitation of the instant elms 41 and 42 because SEQ ID Nos. 1 and 3 encode for the same proteins of SEQ ID Nos:202 and 204 of the instant claims. (See Table 3 of the '119 application and Table 3 of the instant spec. for SEQ ID No correspondence between the specific polynucleotides and polypeptides).
>
> Similarly, claims 43 and 44 recite method using the specific SEQ ID Nos, which read on the instant claimed method of clms 41 and 42.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants disagree with the Examiner's allegation and assert the instant claims are patentably distinct from the claims in co-pending, and co-owned USSN 10/348,119. However, Applicants note that the Examiner's rejection is "provisional" because the alleged conflicting claims have not in fact been patented, and in accordance with MPEP 804(I)(B), no action is currently required on behalf of Applicants.

Applicants believe that all of the Examiners rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

A one-month extension is hereby requested pursuant to 37 CFR §1.136(a). Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $120 for payment of the extension fee.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,

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